REVIEW

Duration of the patient interval in breast cancer and factors associated with longer delays in low-and middle-income countries: A systematic review with meta-analysis

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Abstract

Objective: Breast cancer survival is lower in low- and middle-income countries (LMICs) partially due to many women being diagnosed with late-stage disease. The patient interval refers to the time elapsed between the detection of symptoms and the first consultation with a healthcare provider and is considered one of the core indicators for early diagnosis and treatment. The goal of the current research was to conduct a meta-analysis of the duration of the patient interval in LMICs and investigate the socio-demographic and socio-cultural factors related to longer delays in presentation.

Methods: We conducted a systematic review with meta-analysis (pre-registered protocol CRD42020200752). We searched seven information sources (2009–2022) and included 50 articles reporting the duration of patient intervals for 18,014 breast cancer patients residing in LMICs.

Results: The longest patient intervals were reported in studies from the Middle East (3–4 months), followed by South-East Asia (2 months), Africa (1–2 months), Latin America (1 month), and Eastern Europe (1 month). Older age, not being married, lower socio-economic status, illiteracy, low knowledge about cancer, disregarding symptoms or not attributing them to cancer, fear, negative beliefs about cancer, and low social support were related to longer delays across most regions. Longer delays were also related to use of alternative medicine in the Middle East, South-East Asia, and Africa and distrust in the healthcare system in Eastern Europe.

Conclusions: There is large variation in the duration of patient intervals across LMICs in different geographical regions. Patient intervals should be reduced and, for this purpose, it is important to explore their determinants taking into account the social, cultural, and economic context.

1 | INTRODUCTION

Female breast cancer was the leading cause of global cancer incidence in 2020, responsible for 2.3 million new cases and representing 11.7% of all cancer cases worldwide.[1] Whereas breast cancer incidence is higher in high-income countries, incidence rates are on the increase in low- and middle-income countries (LMICs) due to multiple factors. Some of those are the adoption of Western lifestyles associated with obesity and physical inactivity, the postponement of childbearing, the decline in birth rates, and the reduction of the duration of breastfeeding, all factors that increase the risk of breast cancer.[1,2]

Mortality rates from breast cancer are 17% higher in LMICs.[1,3] Breast cancer survival is lower in LMICs partially due to the scarcity of early detection programs and the large proportion of women presenting with late-stage disease at diagnosis.[2] The lack of adequate diagnosis and treatment facilities and delays associated with diagnosis and treatment are some of the principal reasons contributing to survival differences between high and LMICs.[2,3] Recently, the Global Breast Cancer Initiative was launched aiming to reduce global breast cancer mortality and disparities by increasing access to breast cancer early diagnosis and prompt comprehensive cancer management.[4]

In breast cancer, longer times to diagnosis have been associated with more advanced stage at diagnosis and lower survival[5] and longer times to initiate curative treatment have been associated with higher mortality.[6] Because screening programs are still scarce in LMICs, efforts to promote early presentation and detection of symptomatic breast cancer are key for reducing its burden.[2]

The Model of Pathways to Treatment defines the different phases of the journey of cancer patients from noticing symptoms to diagnosis and treatment start.[7,8] In this model, the *patient interval* refers to the time elapsed between the detection of bodily changes (symptoms) and the first consultation with a healthcare provider (presentation). The patient interval is considered as one of the core indicators for early diagnosis and treatment by the World Health Organization[9] because it is an important contributor to the total time elapsed between the moment cancer becomes detectable due to symptoms and the start of treatment.

Previous research has shown that patient intervals are longer in lower-income countries for a variety of cancers, including breast cancer.[10,11] This has been related to diverse psychosocial factors including the use of traditional, complementary or alternative medicine (TCAM), higher stigma of cancer treatment, shame and stigma associated with cancer (e.g., fear of social rejection), low knowledge of cancer, and diverse health access barriers.[12] In the case of female cancers in particular, women in some cultures may face additional barriers such as the need to ask for family permission.[12]

Previous reviews of patient intervals in breast cancer and the associated personal, social, and psychological factors influencing delays in LMICs have shown that there is large variation not only in the duration of intervals but also in the factors associated.[13–15] It has been proposed that conflicting results may be due to the large cultural and economic diversity that exists within the developing world[14] and the low methodological quality and consistency of the evidence available.[15] In addition, the majority of studies report the median duration of patient intervals but until recently there was no validated methodology available to combine study-specific medians and no previous review reported a meta-analysis. Hence, the first aim of the current review was to provide pooled meta-analytic estimates for the duration of the patient interval in breast cancer in LMICs, taking into account the income level of the countries, the region, and the methodological quality of studies. The second aim was to provide a narrative synthesis of the socio-demographic and socio-cultural factors related to longer delays for the different world regions.

2 | METHOD

We followed PRISMA 2020 guidelines in conducting and reporting the systematic review.[16] This review is based on a larger review considering multiple cancer sites (pre-registered protocol CRD42020200752).[10]

A librarian designed and implemented a search strategy in MEDLINE (via Ovid), Embase, and Web of Science (WOS)-Core Collection (see Supplementary Text 1). Google Scholar, OpenGrey, EThOS, and ProQuest Dissertations & Theses were also searched to identify grey literature. The period searched was January 2009 to May 2022. The start date was chosen based on the date of publication of the Olesen Model[17] and the Model of Pathways to Treatment[18] (two key publications about the different intervals on the cancer care pathway) and with the purpose to include only fairly recent evidence. There were no restrictions by language or country. Additional studies were identified by reviewing the reference lists of relevant studies identified from the search.

2.1 | Eligibility criteria

For the larger review, studies reporting data on the length of any of three intervals on the cancer care pathway (i.e., patient, diagnostic, and pre-treatment) for any cancer site in adult cancer patients presenting with primary cancers were considered. Only studies of symptomatic patients were considered (i.e., excluding screening or accidentally detected cancers). Articles not reporting the results of

original studies, qualitative studies, studies reporting on patients with relapsed cancer, studies reporting on children, adolescents and/or young adults (defined as mean sample age<30 years), studies reporting hypothetical intervals (e.g., from surveys with healthy populations), and studies in languages not understood by the research team were excluded.

For the current review, we further selected those articles that reported data on the patient interval for women diagnosed with breast cancer and residing in LMICs (i.e., countries with a Gross National Income per capita, calculated using the World Bank Atlas method, of $12,695 or less in 2020[19]). Studies reporting only on patients with pregnancy-associated breast cancer were further excluded.

The patient interval was defined according to the Aarhus statement[8] as time in days from the date of first symptom to the date of first presentation, that is, first contact with a healthcare professional. To be included, studies had to report at least the median or mean duration of the interval in days (weeks and months were converted to days, multiplying by 7 and 30, respectively) and the number of patients.

2.2 | Article selection

The Covidence software (https://www.covidence.org) was used to conduct the review. Two reviewers performed independent and blind screening of 26% of the abstracts retrieved. Agreement was satisfactory against the pre-established criterion of >90% (i.e., agreement for the different pairs of reviewers varied between 87% and 100%), and after discussion of disagreements abstract screening was continued individually.

Two reviewers blinded to each other's decisions independently screened the full text of the selected studies against the eligibility criteria. Disagreements were resolved by discussion or a third reviewer. The reasons for exclusion of each article were documented.

2.3 | Data extraction

The data extraction was performed independently by two reviewers blinded to each other's decisions and disagreements were resolved by a third reviewer. For each study, we recorded the year of publication, country, total number of patients with data on the duration of the patient interval, study setting, data sources (i.e., questionnaires, interviews, and/or medical records), study design, inclusion and exclusion criteria.

For the patient interval, the following statistical information was recorded if available (in days): median, interquartile range, minimum, maximum, mean, standard deviation, sample size (N), country, year of start and finish of data collection.

Following the categorization of a previous review,[14] we also extracted, if available, information on the socio-demographic and socio-cultural variables that were significantly associated with the patient interval in each article. Socio-demographic variables included age, any measure of socio-economic status (e.g., income, employment, education...), literacy, marital status, residence, and access to healthcare (e.g., distance of residence to health facilities or availability of health insurance). Socio-cultural variables included those related to the social circumstances of individuals (e.g., availability of social support), or psychological variables such as beliefs, perceptions, symptom interpretation, or knowledge. This information was extracted by one reviewer and thoroughly checked for accuracy by another reviewer. Disagreements were resolved by the first author who acted as arbiter. Information on the factors associated was extracted when authors reported a significant association with the patient interval (e.g., p value < 0.05 or significant confidence intervals (CI) excluding the null value), regardless of how the patient interval was analyzed (e.g., dichotomized or continuous) or the type of analysis (adjusted or unadjusted for potential confounders). To facilitate interpretation, information was extracted in a way that described variable values or categories associated with a relatively 'longer patient interval', as defined by the article authors.

2.4 | Risk of bias

Risk of bias was assessed with the 'Aarhus checklist'[8] developed to evaluate the quality of studies reporting intervals on the cancer treatment pathway (available in Supplementary Text 2). It includes 15 questions about interval definitions, measurement, use of theoretical frameworks, discussion of validity, biases, and limitations of measurement, among others. The answer options for each question were 'yes', 'no', 'uncertain', or 'not applicable'. Each 'yes' response received 1 point ('no' and 'uncertain' received 0 points each) and the proportion of 'yes' responses out of the total that applied was calculated as a measure of risk of bias, where a higher score indicates better methodological quality. Studies with <25% were considered high risk and studies with ≥75% low risk, with the rest considered intermediate.

The risk of bias evaluation was performed independently by two reviewers blinded to each other's decisions and disagreements were resolved by a third reviewer.

2.5 | Synthesis of results

To estimate the pooled duration of the patient interval, a meta-analysis was conducted with the 'metamedian' package in R.[20] Specific study medians (or means) were combined in a pooled median and 95% CI were calculated by inverting the sign test for the median and using the large sample normal approximation of the test statistic.[20] This was done for all studies together, as a function of income level of the country based on Gross National Income (GNI) ('low' with less than $1,046, 'lower-middle' between $1046 and $4,095, and 'upper-middle' between $4096 and $12,695),[19] and as a function of geographical region. The meta-analytical methods for medians do not provide an

estimate of heterogeneity, however, we used the 'median of medians' method which is more suitable for heterogenous data.[20] As an additional measure of the socio-economic level of countries and specifically for illustrative purposes in figures, we also used the Human Development Index (HDI) of each country for the corresponding year of data collection of each study. The HDI combines three dimensions of human development including a long and healthy life (measured by life expectancy at birth), knowledge (measured by expected years of schooling and mean years of schooling) and a decent standard of living (measured by GNI per capita), with a higher value of the index indicating a more advanced stage of development.[21]

The 'metamedian' package can reliably estimate a pooled median when the mean is reported instead of the median.[20] However, using means as medians can introduce bias when means are not a good approximation of the medians (i.e., due to a skewed distribution). For this reason, as sensitivity analysis we repeated the main analysis after excluding studies that only reported means. We also estimated the pooled median duration after excluding studies with high risk of bias and the smallest and largest studies.

To synthetize the results regarding the socio-demographic and socio-cultural factors associated to longer patient intervals, a narrative synthesis was conducted for each region.

All materials, raw data, and analysis code used in the current manuscript are available on the Open Science Framework (OSF): https://osf.io/xbj9z/, DOI 10.17605/OSF.IO/XBJ9Z.

3 | RESULTS

The initial search identified 12,140 records and after applying the eligibility criteria 50 articles reporting on 18,014 breast cancer patients were included in the current review (see Figure 1 for details). Individual exclusion reasons for articles excluded in the full text stage are found on OSF. Detailed information about each article is included in Table S1. The majority of articles reported on studies conducted in countries in Africa (32%),[22–37] followed by South-East Asia (30%),[38–51,71] the Middle East (20%),[52–61] Latin America (16%),[62–69] and Eastern Europe (2%).[45,70] Two articles reported on patients from more than one country.[24,45]

The majority of studies (90%) used interviews with patients and healthcare providers as sources of information and 42% used medical records (32% used a combination of both sources). Due to the retrospective report of the patient interval data (i.e., recalling the dates of first symptom and first consultation), all studies had cross-sectional designs, with two embedded in case-control studies.[27,31] All studies were conducted in a hospital/clinic setting with the exception of one, which was an international survey of patients.[45]

The average methodological quality score (i.e., the percentage of 'Yes' responses from the total items that applied for each study) according to the Aarhus checklist was 45%. In particular, 9 studies (18%) received a high, 39 (78%) medium, and only 2 (4%) low risk of bias rating. For 31 articles (62%) the research team judged that the interval definitions provided were precise, transparent, and reproducible; 34 (68%) studies fully described the healthcare context of the study; 12 (24%) acknowledged the need for theoretical validation or made a reference to a theoretical model underpinning the measurement of intervals and time points; 28 (56%) discussed possible biases in the measurement of the date of first symptom and 9 (18%) discussed the complexity of establishing the date of first presentation (for detailed scores see Table S2).

3.1 | Meta-analysis

There was large variation in the median duration of the patient interval between studies with medians ranging between 6 and 390 days (inter-quartile range of 95 days). Considering all studies, the pooled duration of the patient interval was 50 days (95% CI 34–90), $k = 65^1$.

After excluding studies with high risk of bias, the pooled estimate was 44 days (95% CI 34–70), $k = 56$ (of which $k = 2$ of low risk and $k = 54$ of medium risk) (see also Figure S1). The pooled median from studies with high risk of bias was 154 days (95% CI 31–321), $k = 9$.

The studies also varied in terms of their sample size. In particular, the sample size distribution had a median of 231 participants, with 25% of studies having 158 or fewer participants (Q1) and 25% having 340 or more participants (Q3). After excluding small studies, the pooled median was 40 days (95% CI 31–61), $k = 48$. The pooled median patient interval from small studies ($n \leq 158$) was 128 days (95% CI 64–153), $k = 17$; from medium-sized studies (n between 159 and 339) was 43 days (95% CI 30–72), $k = 31$; and from large studies was ($n \geq 340$) 34 days (95% CI 30–70), $k = 17$ (see also Figure S2).

Finally, after excluding studies that reported means and not medians, the pooled median for the patient interval was 43 days (95% CI 30–66), $k = 48$.

In summary, the duration of the patient interval was significantly longer in studies with high risk of bias, studies with small sample sizes, and studies that reported means and not medians.

3.2 | Analyses by income level

Figures 2 and 3 illustrate that this duration also varied greatly depending on the income level of the country. In particular, patient intervals were longest in low-income countries (140 days (95% CI 88–273), $k = 7$) followed by lower-middle income (91 days (95% CI 36–128), $k = 32$), and shortest in upper-middle income countries (34 days (95% CI 27–43), $k = 26$). This pattern was maintained after excluding studies with high risk of bias (135 days (95% CI 67–315), $k = 6$ in low-income countries; 90 days (95% CI 37–124), $k = 25$, in lower-middle income, and 34 days (95% CI 25–42), $k = 25$, in upper-middle income countries) and after excluding studies reporting means instead of medians (130 days (95% CI 67–270), $k = 6$, in low-income countries; 65 days (95% CI 31–121), $k = 21$, in lower-middle income countries; and 30 days (95% CI 21–46), $k = 21$, in upper-middle income countries).
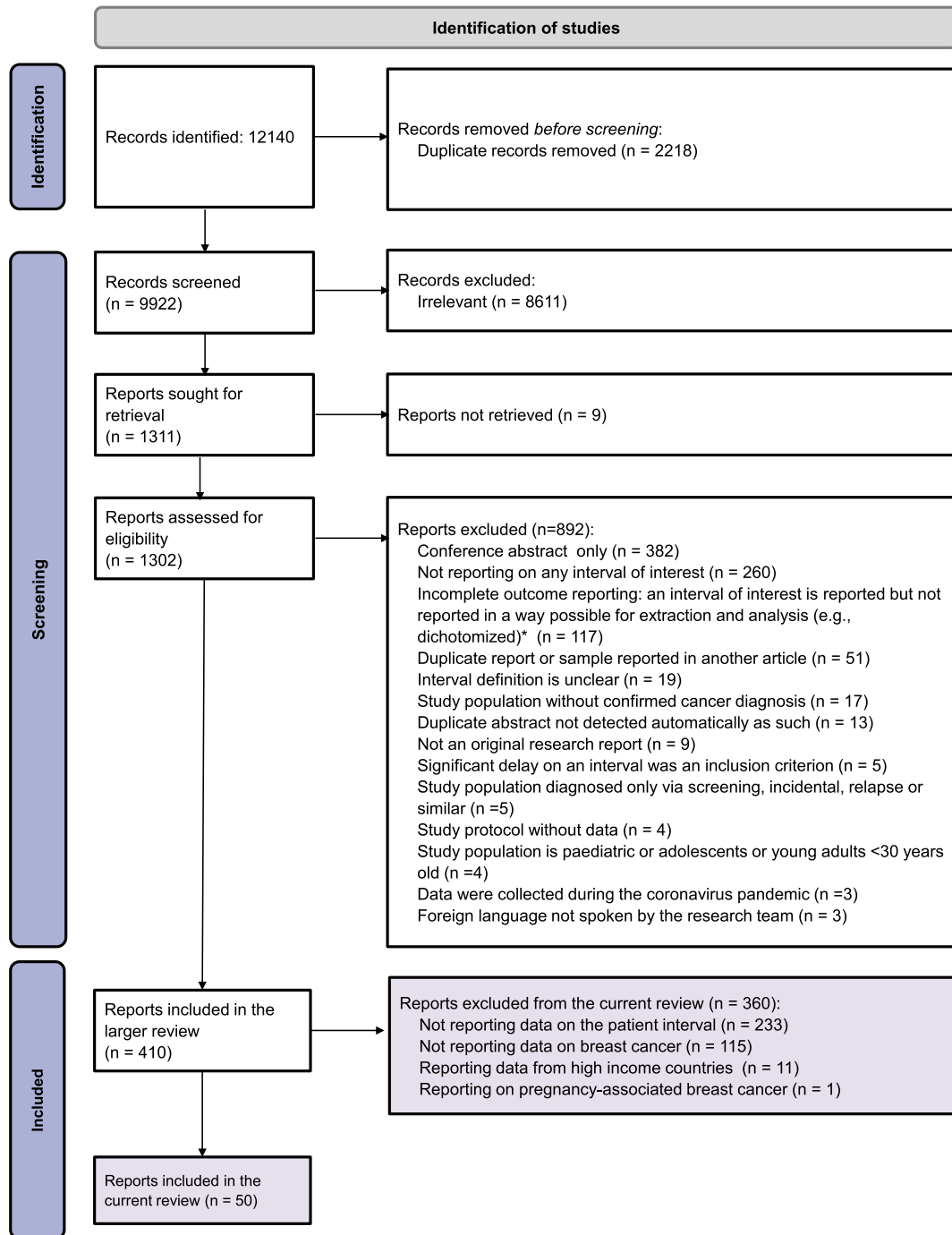
FIGURE 1 Flow chart of the review selection process

3.3 | Analyses by region and factors associated with longer patient intervals

Because there was large variation in the duration of the patient intervals between regions, and because of the important cultural and healthcare variability, we synthesized the results as a function of region. Patient intervals were longest in Middle-Eastern countries, followed by Africa, South-East Asia, Latin America, and Eastern Europe (Figure 2). Detailed information regarding the

factors investigated in relation to the patient interval is reported in Table S1.

3.4 | Middle-East

The pooled duration of the patient interval from studies from the Middle East region, representing Pakistan, Iran, Jordan, and Libya, generally varied between 3 and 4 months. Considering all studies, it

k | N | IQR	Sub-group		Pooled median [95% CI]
65 | 18,014 | 95	Overall		50 [34, 90]
56 | 16,611 | 90	Excluding high risk studies		44 [34, 70]
48 | 16,653 | 78	Excluding small studies		40 [31, 61]
48 | 13,241 | 85	Excluding studies reporting means		43 [30, 66]
7 | 1,784 | 83	Low income		140 [88, 273]
32 | 7,240 | 117	Lower-middle income		91 [36, 128]
26 | 8,990 | 27	Upper-middle income		34 [27, 43]
15 | 2,194 |120	Middle East		120 [32, 152]
20 | 4,761 |120	Africa		78 [25, 133]
15 | 5,331 | 81	South-East Asia		61 [39, 120]
9 | 2,557 | 15	Latin America		39 [24, 55]
6 | 3,171 | 2	Eastern Europe		34 [24, 38]

Pooled median (number of days)

FIGURE 2 Pooled median duration in days and 95% confidence intervals (CI) for the patient interval of breast cancer patients from low- and middle-income countries. k = number of studies or estimates combined in meta-analysis (note that the total does not equal the number of articles in the review because some articles reported data from multiple countries or by subgroups). N = number of patients. IQR, interquartile range of the combined medians. High risk studies were those with scores <25% on the Aarhus checklist. Small studies were studies with samples sizes lower or equal to the first quartile of the sample size distribution of all available studies ($n \leq 158$).

FIGURE 3 Study-specific duration in days of the patient interval (log-transformed) as a function of the country human development index (HDI) and gross national income (GNI)

was 120 days (95% CI 32–152), $k = 15$. It was 105 days (95% CI 31–134), $k = 10$, after removing studies with high risk of bias, and 89 days (95% CI 30–128), $k = 11$, after removing studies that reported means only.

Six out of the ten articles from this region[52–61] investigated factors associated with the duration of the patient interval in patients from Jordan,[53] Pakistan,[55,56,58,60,61] and Iran.[52,59] Lower socio-economic status, education, or income, lower literacy, lack of health insurance, and residing in less densely-populated (i.e., rural) areas were consistently related to longer patient intervals. Socio-cultural variables related to longer patient intervals were explored in four articles and included vague symptom interpretation,[58] lack of knowledge about cancer and cancer symptoms, not believing that cancer is curable, being unfamiliar with breast self-examination,[52] and use of complementary or alternative medicine.[60] One article documented effects of fear of cancer, spouse behavior, and carelessness on the patient interval but did not specify the direction or meaning of the effects (e.g., whether fear of cancer was related to longer or shorter patient intervals).[59]

3.5 | Africa

The pooled duration of the patient interval from studies from Africa, representing Algeria, Ethiopia, Morocco, Nigeria, Rwanda, South Africa, Tunisia, Uganda, and Zambia, varied generally between 1 and 2 months. Considering all studies it was 78 days (95% CI 25–133), $k = 20$. It was 65 days (95% CI 24–118), $k = 17$, after removing studies with high risk of bias, and 39 days (95% CI 21–110), $k = 17$, after removing studies that reported means only.

Twelve out of 16 articles from this region[22–32,34–36] investigated factors associated with the patient interval in Ethiopia,[22,34,35] Morocco,[23,36] Nigeria,[26,27] Rwanda,[29] South Africa,[30] Tunisia,[31] Uganda,[32] and multiple African countries.[24] Older age, lower education, socio-economic status, or literacy, and rural residence were all associated with longer patient delays. Use of traditional medicine,[29,35] low knowledge about breast cancer and self-examination,[22,23] not attributing symptoms to cancer or not considering them as serious,[24,30,32] and not having social support[31,32] were all associated with longer patient delays. One study found that having been prompted by family or friends to seek help was associated with longer delays.[30]

3.6 | South-East Asia

The pooled duration of the patient interval from studies from the South-East Asia region, representing Bangladesh, China, India, Malaysia, Sri Lanka, and Thailand, was about 2 months, specifically 61 days (95% CI 39–120), $k = 15$. There were no studies with high risk of bias. After removing studies that reported only means, the pooled patient interval was 60 days (95% CI 30–118), $k = 11$.

Ten out of the 15 articles[38–47,50] from this region investigated what factors were associated with the duration of the patient interval

in patients from Bangladesh,[71] India,[40–43,45] China,[38,39,46,47] Malaysia,[50] and Thailand.[44] Older age, lower literacy, rural residence, and lower education or income were generally related to longer patient intervals (with the exception of one study that found that higher income was related to longer patient delay in Thailand[44]). Use of alternative medicine,[71] having sought help after advice from family or friends,[44] not having disclosed the symptoms to others,[47] lower family support, lower health values, high external locus of control, lower perceived health competence,[46] distrust in the healthcare system, and disregard or trivialization of discovered symptoms[45] were also associated with longer patient delay. Knowledge of breast cancer had conflicting results based on two studies.[46,47]

3.7 | Latin America

The pooled duration of the patient interval from studies from Latin America, representing Colombia, Mexico, Brazil, and Peru, was slightly longer than a month, specifically 39 days (95% CI 24–55), $k = 9$. It was 35 days (95% CI 21–45), $k = 8$, after removing studies with high risk of bias, and 35 days (95% CI 21–45), $k = 8$, after removing studies that reported means only.

Six out of the 8 articles[62–67,69] from this region investigated factors associated to the patient interval in Mexico,[64–66,69] Brazil,[63] and Peru.[67] Lower socio-economic status, education, or income, not having insurance, not being married, and having low material social support[63] were related to longer patient intervals in studies from Latin America.

3.8 | Eastern Europe

The pooled duration of the patient interval from the two articles[45,70] with data from Eastern Europe was 34 days (95% CI 24–38), $k = 6$. There were no studies with high risk of bias. Only one study reported the median duration and it was 16 days (Estonia).[70] The other study reported the mean patient interval duration, which was between 31 and 33 days for Serbia, Russia, Bulgaria, and Lithuania, and 42 days for Romania.[45]

Older age, lower education, unemployment, and living in less populated areas were all related to longer patient intervals.[45,70] Distrust in the healthcare system and successful therapy, disregard or trivialization of the discovered symptoms,[2] lower fear of disease, and lack of support from family members or friends were the socio-cultural factors significantly associated with longer patient intervals.[45]

4 | DISCUSSION

This review shows that patient intervals in LMICs are generally long and there is large variation depending on the income level of the countries, world region, and study characteristics. In particular, median duration of the patient interval was 4–5 months in low-income

countries, 2–3 months in lower-middle income countries, and 1 month in upper-middle income countries. Thus, the largest difference was observed between upper-middle-income countries and the rest. In addition, results for upper-middle-income countries are comparable to those found for high-income countries in a recent review, where the median patient interval of breast cancer patient was found to be 1 month.[10] This income gradient for breast cancer is in line with the findings of a previous review focused on LMICs that found similar results considering all types of cancer.[11]

The longest patient intervals were reported in studies from the Middle East (about 3–4 months), followed by South-East Asia (2 months), Africa (1–2 months), Latin America (1 month), and Eastern Europe (1 month). This variation may be due to a multitude of causes including patient-related and health system-related factors and cultural diversity. The wide CI for the pooled estimates illustrate the large variation that exists in the estimated patient intervals within regions. This is in line with previous reviews have documented large variability in patient intervals, for instance, within African countries.[13,15] The diverse sensitivity analyses conducted helped partial out some of the contributors to this variability. In particular, we found that patient intervals were longer in studies that had smaller sample sizes, reported means instead of medians, and had lower methodological quality. To illustrate, the patient interval for studies from the African continent was 78 days considering all studies versus 65 days after excluding high risk studies and 39 days after excluding studies that reported means.

The time it takes to reach a breast cancer diagnosis depends on both patient and system-related factors. The NCCN Guidelines for Breast Cancer Screening and Diagnosis (v.1 2022) recommend that individuals should be familiar with their breasts and promptly report changes to their health care provider.[72] The patient interval, measured as the time elapsed between the detection of symptoms and the first presentation to a healthcare professional, can reflect help-seeking delays attributable to the patient, her family, and/or their social network, However, it should be acknowledged that health system-related factors can also contribute to its length directly or indirectly (e.g., through long waiting times for an appointment or via perceptions of the healthcare system that influence help-seeking).[8] After presentation to a healthcare provider, as a function of patient characteristics and the specific symptoms, either (a) a prompt diagnostic workup or (b) waiting (e.g., 1 or 2 menstrual cycles) may be recommended.[72] The time it takes to reach a final diagnosis can then depend not only on the choice of diagnostic evaluation but also on additional healthcare system factors such as scheduling delays and availability of resources, among others.

In contrast to a systematic review on breast cancer published in 2012 that found some contradictory results,[14] the current review found relatively homogenous findings with regard to socio-demographic and health access factors related to the patient interval. In particular, older age, not being married, lower socio-economic status (i.e., lower income or education), and low literacy were all consistently related to longer delays until presentation across all regions. In addition, more difficult access to care such as not having

insurance or residing in less densely populated (rural) areas were also relatively universal predictors of longer patient intervals. Many of these factors are interrelated. For instance, low health literacy is generally associated with lower education level, no formal employment, lower income, and rural residence among cancer patients residing in LMICs.[11]

There was more variation in the socio-cultural barriers documented. There was less evidence available from Latin American and Eastern European countries, and more research is needed from these regions to understand reasons for delayed presentation. Overall, factors recognized as universal predictors of longer patient delays such as low knowledge about cancer (i.e., about symptoms, breast self-examination…), disregarding symptoms, not attributing them to cancer, and fear and negative beliefs about cancer (i.e., that it is not curable) also emerge as barriers to help-seeking for breast cancer in LMICs.[12,73] Fearful and fatalistic beliefs about cancer in lower income contexts have been found to be usually based on the observed experiences of cancer patients from one's social network.[12] Besides on personal observations, beliefs about cancer can be based on cultural and societal influences[74] that should be taken into account when designing and implementing cancer awareness campaigns and interventions because these are more likely to be more successful if they are culturally adapted.[75]

Use of traditional, complementary or alternative (TCAM) medicine was also related to longer intervals in studies from the Middle East, South-East Asia, and Africa. Previous research has identified use of TCAM as a major barrier to cancer care in LMICs and evidence from qualitative studies shows that it stems from certain causal beliefs, cultural norms, and willingness to avoid biomedical treatment.[12] In low-income contexts, the help from TCAM practitioners is commonly encouraged by friends or family because it is perceived as more trustworthy, affordable, or easier to access; it can also be sought to avoid mastectomy, a treatment that could lead to social exclusion in certain cultural contexts.[12]

Having low social support was associated with longer patient intervals in Africa, South-East Asia, Latin America, and Eastern Europe. Higher social support is associated with diverse health-related behaviors[76] and the size of one's social support network predicts breast cancer progression and mortality.[77,78] It is possible that timelier help-seeking when experiencing breast cancer symptoms among patients with higher social support could contribute to these protective effects.

Two studies from Africa and South East Asia found that patient intervals were longer among those patients who were prompted by friends or family to seek help. This finding may seem contradictory to the effect of social support. However, it is possible that it is exactly the involvement of friends or family that led the person to seek help at all in the first place. Unfortunately, the few details provided on how exactly the items were phrased do not permit us to conclude this with certainty.

Finally, distrust in the healthcare system emerged as one of the universal and strongest predictors of delayed help-seeking in several countries in Eastern Europe.[45] Distrust in authorities in general and

the health system in particular are common in this region. A striking example from the context of cancer is the HPV vaccine campaign to prevent cervical cancer in Romania a decade ago, when coverage plummeted to 2.5% of eligible girls, attributed to mistrust and conspiracy theories.[79]

4.1 | Study limitations

We coincide with the conclusions of a recent scoping review that cancer care pathway studies on breast cancer vary considerably in the use of terminology and the assessment of intervals.[15] Hence, a possible limitation of the current review is the possibility to have missed eligible articles despite the broad search criteria. Our review is also limited by the inherent complexity and many possible biases in the measurement of time points and intervals in the cancer treatment pathway[8] and the low frequency of use of validated methods and tools.[15] In addition, the questionnaires used to measure the factors examined in relation to patient intervals were also often poorly described, making interpretation difficult. One of our inclusion criteria was that studies reported the median or mean duration of the patient interval, a criterion that implicitly excludes qualitative studies and studies not reporting these statistics.

Only two studies received a low risk of bias rating on the Arhus checklist and scores were generally quite variable, confirming that further efforts are needed to standardize the measurement and reporting of intervals.[8] The duration of intervals was generally reduced when studies with high risk of bias, small studies, and studies reporting means but not medians were excluded. The latter is due to the typically positively skewed distribution of time-to-event data where the mean is larger than the median. These findings emphasize the advantages of the stratified sensitivity analysis that was conducted for the correct synthesis, interpretation, and comparisons of the available data.

4.2 | Clinical implications

Despite the significant and rising burden of breast cancer in LMICs, data on the duration of patient intervals and the socio-demographic and socio-cultural factors related to longer delays accrued in the past decade are relatively scant. There is large variation within LMICs and patient intervals and their determinants should be studied taking this variation into account. This review shows that how long patients wait until their first consultation with a healthcare professional varies based on the economic level of the country and the region. Older age, not being married, lower socio-economic status, illiteracy, low knowledge about cancer (i.e., about symptoms, breast self-examination), disregarding symptoms, not attributing them to cancer, fear, negative beliefs about cancer, and low social support were related to longer delays across most regions. Additional associations with delay emerged for the use of TCAM in the Middle East, South-East Asia,

and Africa and distrust in the healthcare system in Eastern Europe. Cancer prevention and screening programs are still scarce in LMICs. Efforts to promote early presentation and detection of symptomatic breast cancer by addressing social, psychological, and cultural determinants to reduce the patient interval are key for reducing its burden.[2]

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are openly available in Open Science Framework at https://osf.io/xbj9z/, reference number 10.17605/OSF.IO/XBJ9Z.

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ENDNOTES

[1] Please note that the number of estimates (*k*) joined in meta-analysis may not coincide with the number of articles because some articles reported data on several countries or separately based on another grouping variable for the included sample of patients.

[2] This relationship was the opposite for Romania: high disregard was related to shorted patient intervals in this country.

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